Received: 11 February 2022 | Revised: 20 May 2022 | Accepted: 31 May 2022

DOI: 10.1111/acem.14545

ORIGINAL CONTRIBUTION

High prevalence of fluoroquinolone-resistant UTI among US emergency department patients diagnosed with urinary tract infection, 2018–2020

Brett A. Faine PharmD, MS[1] | Megan A. Rech PharmD, MS, BCPS, BCCCP, FCCM[2] | Priyanka Vakkalanka PhD[3] | Alan Gross PharmD[4] | Caitlin Brown PharmD[5] | Stephanie J. Harding PharmD, BCPS-AQ ID[6] | Giles Slocum PharmD[7] | David Zimmerman PharmD[8] | Anne Zepeski PharmD[9] | Stacey Rewitzer PharmD[10] | Gavin T. Howington PharmD, BCCCP, BCPS[11] | Matt Campbell Pharm.D, BCPS, BCCCP[12] | Jordan Dawson PharmD, BCPS, BCCCP[13] | Cierra N. Treu PharmD, BCCCP[14] | Lucas Nelson PharmD[15] | Mandy Jones PharmD, MPAS, BCPS[16] | Tara Flack PharmD, BCCCP[17] | Blake Porter PharmD, BCPS[18] | Preeyaporn Sarangarm PharmD[19] | Alicia E. Mattson PharmD, BCCCP[20] | Abby Bailey PharmD, BCCCP[21] | Gregory Kelly PharmD, MS, BCCCP[22] | David A. Talan MD[23]

[1]Department of Emergency Medicine and Pharmacy, University of Iowa Hospitals and Clinics, Hawkins, Iowa, USA

[2]Department of Emergency Medicine, Loyola University Medical Center, Maywood, Illinois, USA

[3]Department of Emergency Medicine, University of Iowa, Coralville, Iowa, USA

[4]University of Illinois at Chicago College of Pharmacy, Chicago, Illinois, USA

[5]Assistant Professor of Pharmacy and Emergency Medicine, Mayo Clinic School of Medicine and Science, Rochester, Minnesota, USA

[6]Infectious Diseases Clinical Pharmacy Specialist, Wesley Medical Center, Wichita, Kansas, USA

[7]Emergency Medicine Clinical Pharmacy Specialist, Assistant Professor, Department of Pharmacy Emergency Medicine, Rush University Medical Center, Chicago, Illinois, USA

[8]Associate Professor of Pharmacy at Duquesne University School of Pharmacy, Emergency Medicine Pharmacist at University of Pittsburgh Medical Center-Mercy Hospital, Pittsburgh, Pennsylvania, USA

[9]Emergency Medicine Clinical Pharmacist, University of Iowa, Iowa City, Iowa, USA

[10]Methodist Hospital, St. Louis Park, Minnesota, USA

[11]Department of Pharmacy Practice and Science, University of Kentucky College of Pharmacy, Emergency Medicine Clinical Pharmacy Specialist, Lexington, Kentucky, USA

[12]Emergency Medicine Clinical Coordinator, Department of Pharmacy, Cleveland Clinic, Cleveland, Ohio, USA

[13]Emergency Medicine and Critical Care, Denver Health Medical Center, Denver, Colorado, USA

[14]New York-Presbyterian Brooklyn Methodist Hospital, Brooklyn, New York, USA

[15]Emergency Center Pharmacist Lead, Park Nicollet, Methodist Hospital, Saint Louis Park, Minnesota, USA

[16]Emergency Medicine Clinical Pharmacy Specialist, UK HealthCare, Fellow, Center for Interprofessional Healthcare Education, University of Kentucky, Lexington, Kentucky, USA

[17]Emergency Medicine Clinical Pharmacist, Indiana University Health Methodist Hospital, Indianapolis, Indiana, USA

[18]Emergency Medicine Pharmacist Clinician, University of Vermont Medical Center, Burlington, Vermont, USA

[19]University of New Mexico Hospital, Albuquerque, New Mexico, USA

Supervising Editor: Dr. Brigitte Baumann

[20]Emergency Medicine Clinical Pharmacist, Instructor of Pharmacy, Mayo Clinic, Rochester, Minnesota, USA

[21]Emergency Medicine University of Kentucky HealthCare, Lexington, Kentucky, USA

[22]Rutgers Ernest Mario College of Pharmacy, Emergency Medicine Clinical Pharmacy Specialist, Robert Wood Johnson University Hospital-New Brunswick, New Brunswick, New Jersey, USA

[23]The David Geffen School of Medicine at UCLA, Chairman Emeritus, Dept. of Emergency Medicine, Faculty, Division of Infectious Diseases, Olive View-UCLA Medical Center, Sylmar, California, USA

Correspondence
Brett A. Faine, PharmD, MS, Clinical Associate Professor, Department of Emergency Medicine and Pharmacy, University of Iowa Hospitals and Clinics, 200 Hawkins Dr. Iowa City, IA 52242, USA.
Email: brett-faine@uiowa.edu

Funding information
SPERO Therapeutics

Abstract

Background: Uropathogen resistance, fluoroquinolone-resistance (FQR), and extended spectrum beta-lactamase (ESBL), has been observed to be emerging worldwide with prevalences above recommended thresholds for routine empirical treatment. The primary aim of our study was to determine the prevalence of FQR from a geographically diverse sample of United States emergency departments (EDs).

Methods: We conducted a multi-center, observational cohort study using a network of 15 geographically diverse US EDs. All patients ≥18 years of age with the primary or secondary diagnosis of urinary tract infection (UTI) in the ED identified using International Classification of Diseases (ICD-10) diagnosis code of cystitis, pyelonephritis, or UTI from 2018 to 2020 were included. We calculated descriptive statistics for uropathogens and susceptibilities. Logistic regression analysis was used to identify antimicrobial resistance risk factors associated with FQR *Escherichia coli*.

Results: Among 3779 patients who met inclusion criteria, median age was 62.9 years (interquartile range [IQR]: 41–77.6) and 76.3% were female. The most common diagnoses were complicated (41.2%) and uncomplicated cystitis (40.3%). *E. coli* was the most common pathogen (63.2%), followed by *Klebsiella pneumoniae* (13.2%) and *Enterococcus* species (5.8%). Across all sites, overall *E. coli* FQ-resistance prevalence was 22.1%, ranging from 10.5 to 29.7% by site. The prevalence of ESBL-producing uropathogen was 7.4%, ranging from 3.6% to 11.6% by site. Previous IV or oral antimicrobial use in the past 90-days and history of a multi-drug resistant pathogen were associated with FQ-resistant *E. coli* (odds ratio [OR] 2.68, 95% confidence interval [CI]: 2.04–3.51, and OR 6.93, 95% CI: 4.95–9.70, respectively). Of the patients who had FQ-resistant *E. coli* or an ESBL-producing uropathogen isolated, 116 (37.1%) and 61 (36.7%) did not have any documented risk factors for resistance.

Conclusion: FQ-resistant *E. coli* is widely prevalent across US sites highlighting the need for ongoing monitoring of antimicrobial resistance and, at some locations, modification of empirical treatments.

INTRODUCTION

Urinary tract infections (UTI) are a commonly treated infection in the emergency department (ED), accounting for approximately 3 million visits annually, and 15% of all outpatient antibiotics in the United States (US).[1–4] Enterobacterales remain the most common cause of UTIs and are associated with increased rates of in vitro resistance to commonly prescribed antibioitics.[5,6] In particular, the prevalence of *Escherichia coli* resistance to commonly prescribed antibiotics such as trimethoprim/sulfamethoxazole (TMP/SMX), fluroquinolones (FQ; e.g., ciprofloxacin and levofloxacin), and beta-lactams has continued to increase in most regions of the United States, and underscores the importance of using local antibiograms for selecting empiric treatment in patients diagnosed with a UTI in the ED.[5,7]

Many geographic regions in the United States are reporting prevalences of FQ-resistant (FQR) and TMP/SMX-resistant Enterobacterales of >10%, with some areas with rates >20%, exceeding threshold rates (>10%) recommended by the Infectious

Diseases Society of America (IDSA) to change from one antibiotic class to another for empirical treatment.[5,6] Additionally, the prevalence of extended spectrum β-lactamase (ESBL)-producing Enterobacterales continues to increase, now exceeding 20% in some US locations.[6]

Given a shrinking armamentarium of effective antibiotic treatment for UTIs, the IDSA and Centers for Disease Control and Prevention (CDC) have identified the need for continued surveillance of resistance patterns at the local and national health care system level as a top priority to best inform antibiotic treatment decisions.[7,8] In 2019, the CDC classified ESBL-producing Enterobacterales as a serious threat due to the increase in community infections.[9] ESBL-producing Enterobacterales are oftentimes also resistant to FQ as well as other agents commonly used to treat UTIs. As antimicrobial resistance can change rapidly, surveillance and reporting of the prevalence of *E.coli* resistant and ESBL-producing uropathogens is necessary to guide empiric antimicrobial treatment. The objective of our study was to determine the prevalence of FQ resistance among patients presenting to the ED and diagnosed with a UTI among a geographically diverse group of US sites. Secondary objectives were to identify geographic variation in *E. coli* resistance and risk factors associated with antimicrobial resistance.

METHODS

We conducted a multi-center, retrospective observational cohort study at 15 geographically diverse, US hospital EDs, that participate in the Emergency Medicine PHARMacotherapy Research NETwork (EMPHARM-NET) (see Figure 1 for full site listings). Patients were identified based on primary diagnosis of uncomplicated or complicated cystitis and uncomplicated or complicated pyelonephritis using International Classification of Diseases (ICD)-10 codes: ICD-10, N30.00, N30.01, and N39.0 between January 1st, 2018 – December 31st, 2020. All patients ≥18 years of age who had a primary or secondary diagnosis of UTI in the ED, reported symptoms of a UTI, and had a urine culture obtained in the ED were included. Exclusion criteria were as follows: pregnancy; suspected or confirmed acute bacterial prostatitis; orchitis, epididymitis; or chronic bacterial prostatitis as determined by history and/or physical examination; gross hematuria requiring intervention other than administration of antibiotics for UTI or removal or exchange of a urinary catheter; and urinary tract surgery within 7 days prior to ED presentation. Patients could only have one ED visit included in the study with subsequent visits being excluded in the study population.

Data Collection

All data variables were defined a priori and were available for abstraction from the electronic medical record (EMR). Data collected included patient-specific characteristics (e.g., age, sex, past medical history, laboratory results), signs and symptoms (e.g., fever, dysuria, flank pain, frequency/urgency) of UTI, risk factors for antimicrobial resistance, ED disposition, and urine microbiological results and susceptibilities. Data were abstracted at each site by the principal investigator (PI) or by a trained data abstractor with an audit of a random sample of charts (~10%) completed to ensure

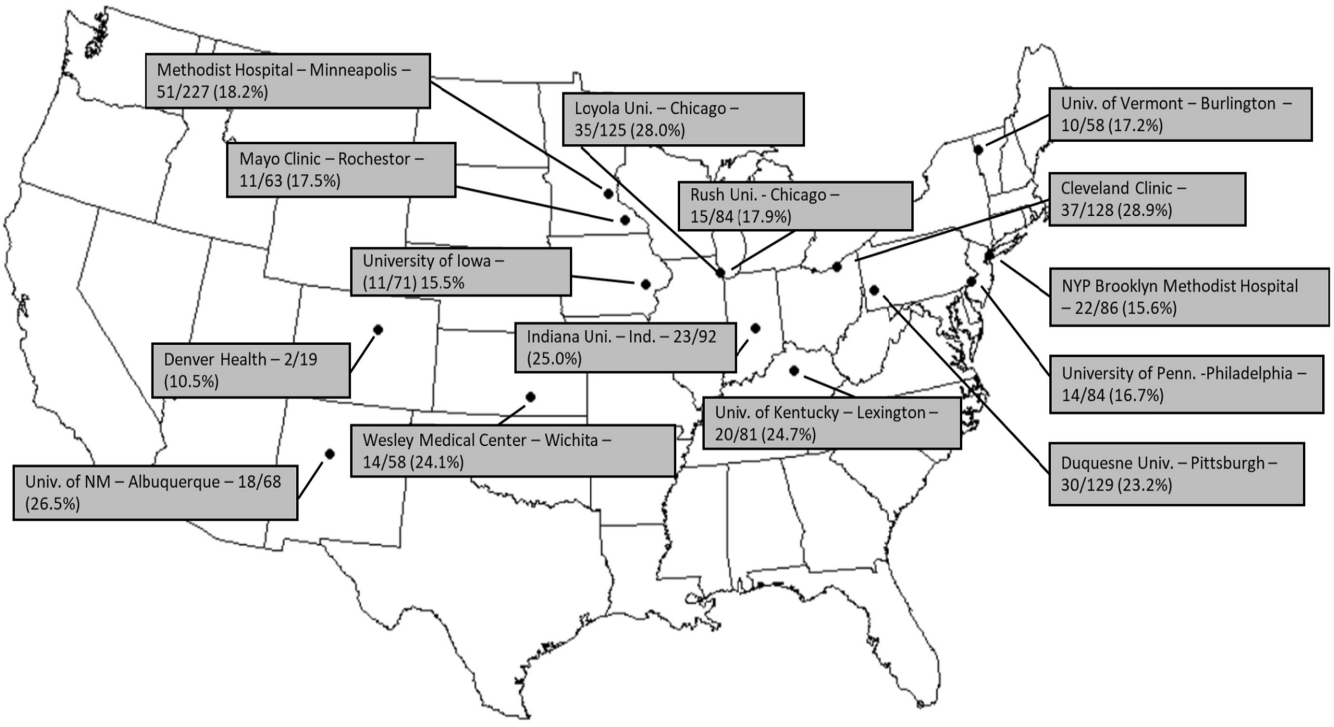

FIGURE 1 Prevalence of fluoroquinolone-resistant *Escherichia coli* based on EMPHARM-NET site location, 2018–2020

that abstractor entries were accurate and complete. All site institutional review boards approved the study. The study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[10] We used REDCap© electronic-data capture tool (Version 6.18.1, 2019; Vanderbilt University, Nashville, TN) hosted by the University of Iowa to manage all study data.[11]

Definitions

Cystitis was defined as patients reporting dysuria, urinary frequency or urgency, suprapubic pain, or hematuria.[12,13] Pyelonephritis was defined as patients reporting urinary symptoms in addition to a fever (temperature > 38°C), chills, flank pain, costovertebral-angle tenderness, and nausea or vomiting.[12,13] Patients were further classified as having complicated urinary tract infections (cystitis or pyelonephritis) if they were male or had a pre-existing anatomical condition or current immunocompromising condition that may increase their risk for treatment failure.[6] Pre-existing urinary tract anatomical conditions were: history of kidney stones, urinary obstruction, neurogenic bladder, renal insufficiency, long-term urinary catheter [indwelling foley or suprapubic catheter], renal transplant, and nephrostomy tubes).[6] Immunocompromising conditions included active cancer, chronic systemic corticosteroid use, current use of immunosuppressants (e.g., renal transplant), and human immunodeficiency virus (HIV) disease. We classified patients without criteria for complicated cystitis or pyelonephritis as uncomplicated infections.

A positive urine culture was defined as a specimen with ≥10^4 CFU/mL bacteria isolated in the urine culture with ≤2 organism isolated in the urine culture.[14–17] If a urine culture grew >2 organisms, it was considered to be contaminated; if no organisms were isolated, it was considered no growth.[5,14] The following pathogens were considered to be contaminants: *Lactobacillus*, non-*saprophyticus* coagulase-negative *Staphylococcus*, *Corynebacterium* species; or β-hemolytic streptococci.[14] Contaminated cultures and no growth cultures were reported as a negative culture in the final analysis. To test for the presence of ESBL-Enterobacterales or carbapenemase-producing Enterobacterales, the majority of the sites used VITEK® 2 (bioMerieux) to test for ESBL presence and Xpert® Carba-R (Cepheid) test for the presence of carbapenemases. If the site did not have capability to test specifically for ESBL-producing Enterobacterales, we considered isolates that were non-susceptible to ceftriaxone (i.e., minimum inhibitory concentration [MIC] > 1 μ/ml) to be ESBL producing.[6]

We evaluated risk factors for antimicrobial resistance, which included the following: previous intravenous (IV) or oral antibiotic use in the prior 90 days, hemodialysis dependence, pre-existing urinary tract anatomical conditions as defined above, residence in a long-term care facility, and history (within the past 12 months) of multi-drug resistant (MDR) pathogen in the past 12 months.[18,19] In all cases, the EMR was reviewed for the following MDR pathogens: ESBL-producing Enterobacterales; carbapenem-resistant Enterobacterales (CRE); methicillin-resistant *Staphylococcus aureus* (MRSA); vancomycin resistant Enterococci (VRE); *Stenotrophomonas maltophilia*; *Pseudomonas aeruginosa*; *Acinetobacter* spp.; AmpC-beta-lactamase-producing bacteria; or resistance to antibiotics from three different classes within the past 12 months.

Statistical analysis

Descriptive characteristics were used to characterize overall patient demographics for the total cohort, as well as for culture-positive and culture-negative patients. Among those with positive cultures, we characterized the distribution of uropathogens by UTI type including complicated and uncomplicated cystitis and pyelonephritis. We quantified the prevalence of FQ-resistant *E. coli by participating centers to describe geographical variability. Similarly, we quantified antimicrobial resistant prevalences for E. coli isolates*. We assessed bivariate associations using logistic regression between select demographic and clinical factors on the presence of ESBL and FQ-resistant *E. coli and present odds ratios and 95% confidence intervals (CI). A multivariable analysis was conducted to analyze potential variables associated with the presence of ESBL or FQ-resistant E. coli. Variables identified for regression analysis came from previously identified risk factors (defined above) or were considered clinically significant variables that may be associated with risk of MDR* (e.g., *kidney disease)*. All analyses were conducted using SAS v9.4 (Cary, NC).

RESULTS

Over the 3-year period (January 2018 – December 2020), 3714 patients met inclusion criteria for our study. Of the included patients, 2242 patients (60%) had a urine culture that grew ≤2 uropathogens at ≥10^4 CFU/ml and 1472 had a urine culture that was negative (e.g., no growth or contaminated). Patient median age was 62.9 years (Interquartile range [IQR] 41–77.6 years), 76.1% were female, and 36.7% and 28.8% of patients reported having dysuria and frequent/urgent urinary symptoms, respectively (Table 1). The most common UTI diagnosis was complicated cystitis (41.2%). Most patients (66.2%) were discharged home from the ED. Antimicrobial resistance risk factors were identified in 44.2% of patients, with 15.1% having at least two risk factors; the most common (29.1%) risk factor was IV or oral antibiotic use in the prior 90 days.

Of the patients with a positive urine culture, 84.7% had cultures that grew Enterobacterales with *E. coli* (63.2%) being the most common pathogen isolated (Table 2). Overall prevalences of ESBL-producing and carbapenemase-producing uropathogens were 7.4% and 0.3%, respectively.

For the primary outcome, 22.1% of *E. coli* isolates showed resistance to FQs (Table 3). Overall, *E. coli* resistance was most prevalent to ampicillin (39.2%) and TMP/SMX (24.3%). Of patients with *E. coli*, resistance to carbapenems (e.g., meropenem, imipenem, ertapenem) was reported in 0.3% of patients. FQ-resistant *E. coli* occurred

TABLE 1 Characteristics of patients diagnosed with a urinary tract infection from 15 US EDs

Demographic and clinical characteristics	Overall (*N* = 3,714)		Culture positive (*N* = 2,242)		Culture negative (*N* = 1,472)	
Demographics						
Age in years, median (IQR)	62.9	(41.0–77.6)	66.0	(45.5–79.4)	58.1	(36.3–74.0)
Sex, *n* (%)						
Male	885	(23.8)	582	(26.0)	303	(20.6)
Female	2,827	(76.1)	1,659	(74.0)	1,168	(79.3)
Disposition, *n* (%)						
Discharged from ED	2,457	(66.2)	1,329	(59.3)	1,128	(76.6)
Admitted - Non-ICU	1,151	(31.0)	829	(37.0)	322	(21.9)
Admitted - ICU	104	(2.8)	83	(3.7)	21	(1.4)
Clinical history, *n* (%)						
Kidney disease	506	(13.6)	350	(15.6)	156	(10.6)
Advanced liver disease (cirrhosis/ESLD)	67	(1.8)	47	(2.1)	20	(1.4)
Diabetes	989	(26.6)	624	(27.8)	365	(24.8)
UTI characteristics, *n* (%)						
Chief complaint UTI	1,875	(50.5)	1,158	(51.7)	717	(48.7)
UTI Type						
Pyelonephritis, uncomplicated	294	(7.9)	187	(8.3)	107	(7.3)
Pyelonephritis, complicated	393	(10.6)	269	(12.0)	124	(8.4)
Cystitis, uncomplicated	1,495	(40.3)	823	(36.7)	672	(45.7)
Cystitis, complicated	1,532	(41.2)	963	(43.0)	569	(38.7)
UTI symptoms						
Altered mental status	548	(14.8)	381	(17.0)	167	(11.3)
Fever	483	(13.0)	344	(15.3)	139	(9.4)
Dysuria	1,364	(36.7)	795	(35.5)	569	(38.7)
Flank pain	514	(13.8)	304	(13.6)	210	(14.3)
Frequent/urgent urinary symptoms	1,071	(28.8)	642	(28.6)	429	(29.1)
Suprapubic pain	645	(17.4)	406	(18.1)	239	(16.2)
Characteristics that may contribute to antimicrobial resistance, *n* (%)						
Previous IV or oral antibiotic use in the past 90 days	1,080	(29.1)	639	(28.5)	441	(30.0)
Hemodialysis dependence	54	(1.50	34	(1.5)	20	(1.4)
Urinary tract abnormality (e.g., catheter)	583	(15.7)	385	(17.2)	198	(13.5)
Long-term or intermittent urinary catheter	366	(9.9)	262	(11.7)	104	(7.1)
Nephrolithiasis	107	(2.9)	62	(2.8)	45	(3.1)
Renal transplant	42	(1.1)	21	(0.9)	21	(1.4)
Neurogenic bladder	135	(3.6)	107	(4.8)	28	(1.9)
Nephrostomy tubes	51	(1.4)	30	(1.3)	21	(1.4)
Residence in a long-term care facility	280	(7.5)	205	(9.1)	75	(5.1)
History of multi-drug resistant pathogen	385	(10.4)	296	(13.2)	89	(6.0)
Extended spectrum beta-lactamase	128	(3.4)	109	(4.9)	19	(1.3)

TABLE 1 (Continued)

Demographic and clinical characteristics	Overall (*N* = 3,714)		Culture positive (*N* = 2,242)		Culture negative (*N* = 1,472)	
Carbapenem-resistant Enterobacterales	17	(0.5)	10	(0.4)	7	(0.5)
Methicillin-resistant *Staphylococcus aureus*	103	(2.8)	68	(3.0)	35	(2.4)
Vancomycin resistant *Enterococci*	44	(1.2)	31	(1.4)	13	(0.9)
Stenotrophomonas maltophilia	6	(0.2)	5	(0.2)	1	(0.1)
Pseudomonas aeruginosa	69	(1.9)	56	(2.5)	13	(0.9)
Acinetobacter spp.	14	(0.4)	11	(0.5)	3	(0.2)
≥3 different classes	160	(4.3)	128	(5.7)	32	(2.2)

TABLE 2 Pathogens identified based on type of urinary tract infection

		Pyelonephritis		Cystitis	
	Overall (*n* = 3714)	complicated (*n* = 393)	Uncomplicated (*n* = 294)	complicated (*n* = 1532)	Uncomplicated (*n* = 1495)
Uropathogen	***n***	***n***	***n***	***n***	***n***
Enterbacterales					
E. coli	1417 (38.1)	144 (36.6)	139 (47.3)	521 (34.0)	613 (41.0)
E. cloacae	49 (2.2)	6 (1.5)	1 (0.3)	26 (1.7)	16 (1.1)
E. aerogenes	24 (1.1)	3 (0.8)	1 (0.3)	17 (1.1)	3 (0.2)
K. oxytoca	35 (1.6)	3 (0.8)	3 (1.0)	23 (1.5)	6 (0.4)
K. pneumoniae	296 (13.2)	44 (11.2)	21 (7.1)	144 (9.4)	87 (5.8)
Citrobacter spp.	55 (2.5)	8 (2.0)	3 (1.0)	30 (2.0)	14 (0.9)
Proteus spp.	122 (5.4)	17 (4.3)	9 (3.1)	74 (4.8)	22 (1.5)
Non-enterbacterales					
Enterococcus species	130 (5.8)	25 (6.4)	8 (2.7)	70 (4.6)	27 (1.8)
P. aeruginosa	82 (3.7)	18 (4.6)	3 (1.0)	45 (2.9)	16 (1.1)
Staphylococcus aureus	44 (2.0)	8 (2.0)	1 (0.3)	27 (1.8)	8 (0.5)
Staphylococcus saprophyticus	22 (1.0)	3 (0.8)	5 (1.7)	2 (0.1)	12 (0.8)
Multi-drug resistant					
ESBL-producing pathogen[a]	166 (7.4)	32 (8.1)	14 (4.8)	83 (5.4)	37 (2.5)
CRE-producing pathogen[a]	6 (0.3)	1 (0.3)	0 (0.0)	3 (0.2)	2 (0.1)
Other[b]	146 (6.5)	16 (4.1)	6 (2.0)	78 (5.1)	46 (3.1)

[a]The multi-drug resistant pathogens presented consist of a subset of the Enterbacterales pathogens.

[b]Other = pathogens not commonly isolated in the urinary tract but are considered pathogenic (e.g., *Aerococcus urinae*, *Stenotrophomonas maltophilia*, etc.).

in complicated pyelonephritis (33.3%), followed by complicated cystitis (28.2%), uncomplicated pyelonephritis (17.3%), and uncomplicated cystitis (15.3%). (Table 3). There was geographic variation in the prevalence of FQ-resistant *E. coli* ranging from 10.5–29.7%. Fourteen of the enrolling institutions reported FQ-resistant *E. coli* rates >15%, with seven reporting rates >20% (Figure 1).

Use of IV or oral antibiotics in the prior 90 days and a history of having a MDR pathogen were significantly associated with isolating FQ-resistant *E. coli* (aOR, 1.87 [95% CI 1.38–2.53]; aOR, 5.25 [95% CI 3.67–7.51], respectively) (Table 4). History of having a MDR pathogen was significantly associated with isolating an ESBL-producing uropathogen (aOR, 4.71 [95% CI 3.26–6.81) (Table 5). Of the patients who had FQ-resistant *E. coli* or an ESBL-producing uropathogen isolated, 116 (37.1%) and 61 (36.7%) did not have any documented risk factors for resistance.

DISCUSSION

Our study of contemporary patients from 15 centers across the US found that the prevalence of FQ-resistant *E. coli* exceeded 15% at 14 of the 15 sites and was >20% at 7 of the 15 sites signifying that

TABLE 3 Antimicrobial drug resistance prevalence for *Escherichia coli* isolates (2018-2020)[a]

		Pyelonephritis		Cystitis	
	Overall (N = 1,471)	complicated (n = 144)	Uncomplicated (*n* = 139)	complicated (*n* = 521)	Uncomplicated (*n* = 613)
Antimicrobial drug	***n***	***n***	***n***	***n***	***n***
Beta lactams					
Ampicillin/sulbactam	245 (17.3)	28 (19.4)	37 (26.6)	90 (17.3)	90 (14.7)
Ampicillin	556 (39.2)	61 (42.4)	66 (47.5)	208 (39.9)	221 (36.1)
Cefazolin	180 (12.7)	31 (21.5)	19 (13.7)	85 (16.3)	45 (7.3)
Cefepime	83 (5.9)	15 (10.4)	6 (4.3)	38 (7.3)	24 (3.69)
Ceftazidime	45 (3.2)	11 (7.6)	5 (3.6)	20 (3.8)	9 (1.5)
Ceftriaxone	124 (8.8)	22 (15.3)	10 (7.2)	62 (11.9)	30 (4.9)
Ertapenem	2 (0.1)	1 (0.7)	0 (0.0)	1 (0.2)	0 (0.0)
Imipenem	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Meropenem	2 (0.1)	2 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)
Piperacillin/tazobactam	20 (1.4)	7 (4.9)	1 (0.7)	6 (1.2)	6 (1.0)
Aminoglycosides					
Amikacin	5 (0.4)	1 (0.7)	0 (0.0)	2 (0.4)	2 (0.3)
Gentamicin	99 (7.0)	15 (10.4)	8 (5.8)	39 (7.5)	37 (6.0)
Tobramycin	40 (2.8)	14 (9.7)	3 (2.2)	15 (2.9)	8 (1.3)
Fluoroquinolones					
Ciprofloxacin	269 (19.0)	41 (28.5)	22 (15.8)	122 (23.4)	84 (13.7)
Levofloxacin	157 (11.1)	31 (21.5)	14 (10.1)	65 (12.5)	47 (7.7)
Fluoroquinolone resistance[b]	313 (22.1)	48 (33.3)	24 (17.3)	147 (28.2)	94 (15.3)
Other					
Aztreonam	41 (2.9)	10 (6.9)	4 (2.9)	20 (3.8)	7 (1.1)
Nitrofurantoin	28 (2.0)	4 (2.8)	1 (0.7)	17 (3.3)	6 (1.0)
Trimethoprim/ sulfamethoxazole	344 (24.3)	44 (30.6)	46 (33.1)	123 (23.6)	131 (21.4)

[a]These results are from testing conducted at site hospital microbiology laboratories. Not all antimicrobials were tested at each site. Denominators with total tested for each antimicrobial are presented.

[b]Resistant to ciprofloxacin or levofloxacin.

geographic variation exists in *E. coli* FQ-resistance. Patients presenting with a complicated UTI had *E. coli* FQ resistance prevalences that exceeded 50% at many sites, whereas those with uncomplicated pyelonephritis and cystitis had resistance prevalences being 29.3% and 29.9% for pyelonephritis and cystitis, respectively. Previous studies have shown that prevalence of *E. coli* resistance to FQs has been increasing over the past two decades.[20,21] In an analysis of over 12 million urine specimens, *E. coli* resistance to FQs was reported to be 3% in 2000 but increased to 17.1% in 2010.[21] A study enrolling participants from 2013 to 2014 evaluated the prevalence of FQ-resistant *E. coli* in patients presenting to the ED with acute uncomplicated pyelonephritis and found that 19.9% of isolates were resistant.[5] The combined *E. coli* FQ-resistance rate at all sites in this study was 22.1% (range 10.5%–29.7% by site) demonstrating that resistance continues to increase across the US.

The most recent IDSA guidelines (published >10 years ago) for the treatment of uncomplicated pyelonephritis recommend empiric FQ treatment unless the local prevalence of *E coli* resistance is greater than 10%, in which case, an initial parenteral antibiotic (e.g., ceftriaxone, consolidated 24-hour dose of an aminoglycoside) dose is recommended to be administered before the patient is discharged home.[7] All 15 sites in our study reported *E. coli* FQ-resistance >10%, suggesting that empiric antimicrobial regimens should be modified for patients with pyelonephritis. For uncomplicated cystitis, FQ-resistant was reported in 29.9% of all of *E. coli* isolates. Fortunately, current guidelines recommend nitrofurantoin as first-line treatment for uncomplicated cystitis as resistance rates have remained low.[7] In the total cohort, we found *E. coli* resistance to nitrofurantoin was 2%, with it being slightly lower at 1.9% in patients with uncomplicated cystitis suggesting that nitrofurantoin remains a viable treatment option for uncomplicated cystitis.

As FQ-resistant *E. coli* continues to impact empiric treatment options in the ED, of growing concern is resistance emerging to alternative treatments mediated through bacterial production of

TABLE 4 Risk factors associated with isolating FQ-resistant *E. coli*

	FQ Res *E coli*			
Characteristic	**uOR[a]**	**95% CI**	**aOR[b]**	**95% CI**
Sex (ref = female)	1.54	1.13–2.09	1.11	0.78–1.60
Kidney disease	1.91	1.36–2.68	1.37	0.92–2.03
Advanced liver disease (cirrhosis/ ESLD)	0.74	0.25–2.19	0.41	0.13–1.33
Previous IV or oral antibiotic use in the past 90 days	2.68	2.04–3.51	1.87	1.38–2.53
Hemodialysis dependence	2.97	0.90–9.80	0.96	0.21–4.29
Urinary tract abnormality (e.g., catheter)	2.74	1.92–3.91	1.60	0.51–5.00
Long-term or intermittent urinary catheter	3.45	2.25–5.28	1.26	0.42–3.80
Nephrolithiasis	1.13	0.51–2.54	0.64	0.17–2.34
Renal transplant	2.54	0.80–8.07	0.78	0.19–3.22
Neurogenic bladder	3.69	1.93–7.06	1.12	0.46–2.83
Nephrostomy tubes	1.77	0.32–9.71	0.56	0.08–4.04
Residence in a long-term care facility	2.17	1.43–3.31	1.93	1.22–3.07
History of multi-drug resistant pathogen	6.93	4.95–9.70	5.25	3.67–7.51

[a]Represents the unadjusted odds ratios of each risk factor for FQ-resistance among *E coli* isolates ($n = 1471$).

[b]Among patients with positive *E coli* culture, adjusted for all variables listed.

TABLE 5 Risk factors associated with isolating an ESBL-producing uropathogen

	ESBL			
Characteristic	**uOR[a]**	**95% CI**	**aOR[b]**	**95% CI**
Sex (ref = female)	1.29	0.91–1.82	1.16	0.79–1.70
Kidney disease	1.55	1.05–2.29	1.17	0.76–1.80
Advanced liver disease (cirrhosis/ ESLD)	1.17	0.41–3.29	0.82	0.28–2.42
Previous IV or oral antibiotic use in the past 90 days	2.04	1.48–2.81	1.37	0.96–1.95
Hemodialysis dependence	1.68	0.59–4.84	0.78	0.23–2.67
Urinary tract abnormality	1.71	1.18–2.47	1.33	0.52–3.40
Long-term or intermittent urinary catheter	1.60	1.04–2.45	0.79	0.32–1.95
Nephrolithiasis	1.10	0.44–2.78	0.72	0.22–2.31
Renal transplant	4.00	1.45–11.05	2.17	0.64–7.40
Neurogenic bladder	1.79	0.98–3.27	0.78	0.36–1.67
Nephrostomy tubes	1.95	0.67–5.65	0.88	0.24–3.27
Residence in a long-term care facility	1.58	0.98–2.54	1.34	0.81–2.19
History of multi-drug resistant pathogen	5.30	3.77–7.44	4.71	3.26–6.81

[a]Represents the unadjusted odds ratios of each risk factor for ESBL-producing uropathogens among culture positive cohort ($n = 2242$).

[b]Among culture positive patients, adjusted for all variables listed.

ESBLs.[22,23] A recent study evaluating the emergence of ESBL UTI infections among ED patients who were hospitalized reported the prevalence of ESBL-producing Enterobacterales to be 17.2% (range: 4.6%–45.4%).[6] The prevalence of ESBL-producing Enterobacterales in our cohort was significantly lower at 7.4% (range: 3.6–11.6), but is consistent with previous reports evaluating community-associated ESBL infections.[24] The difference in findings can likely be explained by the differing enrollment criteria and the predominance of outpatient treatment. Our study sought to determine resistance rates among all ED patients who were diagnosed with a UTI, whereas Talan et al. evaluated only patients hospitalized for treatment of UTI.[6] Additional differences could be related to the prevalence of risk factors for ESBL-producing Enterobacterales. In the previously mentioned paper, over 75% of the patients had received antibiotic treatment within the prior 90-days, and over 30% had a history of FQ- or ceftriaxone-resistant isolate in the prior 90 days.[6] In contrast, 29.1% of our cohort had received antibiotic treatment within the prior 90-days, and only 10.4% had a history of a MDR pathogen.

It is evident that the prevalence of ESBL-producing uropathogens is increasing, but our results suggest they may be less prevalent in patients who are less ill, being discharged home from the ED, and without any risk factors for MDR pathogens.

As the prevalence of antimicrobial resistance continues to rise among commonly prescribed antibiotics, it is evident that certain patients are at much higher risk for having a UTI caused by a resistant uropathogen. Multiple studies have evaluated the impact of risk factors on the likelihood of having a resistant uropathogen with the most common risks factors associated with isolating a resistant uropathogen being recent exposure (e.g., 60–90 days) to antimicrobial therapy, history of MDR pathogen, and complicating genitourinary factors (e.g., chronic indwelling catheters).[5,25–27] Our research is consistent with the existing literature in demonstrating the importance of identifying those patients with increased risk for resistant organisms, notable those who received an antibiotic in the prior 90 days or had a history of MDR pathogen. Importantly, however, we found that over 1/3 of patients with resistant organisms did not have identifiable risk factors. This has been described in patients hospitalized with UTI and for patients with ESBL, and we also demonstrate that this is also the case for patients with FQ resistance.[6,26] Our results taken together with those of Frazee et al[26] and Talan et al,[5,6] highlight serious concerns with increasing resistance rates to commonly used antibiotic treatments and that resistance impacts patients with and without identifiable risk factors.

STRENGTHS AND LIMITATIONS

Strengths of our study include being a multi-center study conducted at 15 US sites with geographic variation using routinely collected and relatively current (2018–2020) health care data. We used broad inclusion criteria that should be representative of the ED patient population and is more representative of community prevalences. Additionally, because we stratified our patient population, our reported resistance prevalances are more granular based on UTI type (e.g., complicated vs. uncomplicated).

However, our study has several important limitations that must be addressed. First, our study was retrospective and observational, which introduces the prospect of inaccurate documentation. We intentionally selected variables for analysis that are likely to be accurately reported and are easily abstractable from the EMR; however, there may have been slight variation between centers in recording of data. Second, UTIs are one of the most common infectious related diagnoses in the ED and the diagnostic error for UTI in the ED has been reported to be high, which could have impacted our included population.[28] We created inclusion criteria so that patients not only had to have an ICD-10 diagnosis code for UTI during their ED visit, but they also had to have reported symptoms of UTI and urine culture obtained increasing the likelihood of only enrolling patients with a UTI. Third, there is some difficulty in the ability to accurately capture some of the proposed antimicrobial risk factors (e.g., previous antibiotic exposure in past 90-days, history of MDR) because of the nature of the health care system (not a closed system). Fourth, while we have 15 sites included in our study representing various geographic areas across the US, our network lacks sites in the southern and pacific regions decreasing the generalizability of our findings to those regions. Finally, we only included patients presenting to the ED so the generalizability of our resistance findings may be limited.

CONCLUSIONS

FQ-resistant *E. coli* is widely prevalent and ESBL-mediated resistance appears to be increasing across US sites highlighting the need for ongoing monitoring of antimicrobial resistance and, at some locations, modification of empirical treatments.

AUTHOR CONTRIBUTION

Study Concept and Design: B.F., M.R., D.T., A.G. *Acquisition of Data*: A.G., C.B., A.Z., S.R., J.D., L.N., B.P., P.S., A.M., A.B., G.K., B.F., M.R., S.H., G.S., D.Z., G.H., M.C., C.T., M.J., T.F. *Analysis and interpretation of data*: B.F., M.R., P.V., D.T., A.G. *Drafting of manuscript*: A.G., C.B., A.Z., S.R., J.D., L.N., B.P., P.S., A.M., A.B., G.K., B.F., M.R., S.H., G.S., D.Z., G.H., M.C., C.T., M.J., T.F., P.V., and D.T. *Critical revision of manuscript for important intellectual content, statistical expertise, and acquisition of funding*: A.G., C.B., A.Z., S.R., J.D., L.N., B.P., P.S., A.M., A.B., G.K., B.F., M.R., P.V., S.H., G.S., D.Z., G.H., M.C., C.T., M.J., T.F., and D.T.

ACKNOWLEDGMENTS

Keith Burrell, University of Iowa. Devin Spolsdoff, MS, University of Iowa. Joann Huynh, PharmD Candidate (2022), University of Illinois at Chicago College of Pharmacy. Kevin Johns, PharmD Candidate (2022), University of Illinois at Chicago College of Pharmacy. Danielle Garza, PharmD. Monica Frauhiger, PharmD. Lyudmila Garbovsky, PharmD, BCPS, BCCCP, Hospital of the University of Pennsylvania, Philadelphia, PA. David Gajdosik, PharmD, BCPS, Hospital of the University of Pennsylvania, Philadelphia, PA. Rachel Lam, Stritch School of Medicine, Loyola University Chicago. Mollie Shutter, Stritch School of Medicine, Loyola University Chicago.

FUNDING INFORMATION

Some of the work was supported by Spero Therapeutics Investigator Initiated Research Program.

CONFLICT OF INTEREST

The following authors report no conflict of interest: A.G., C.B., A.Z., S.R., J.D., L.N., B.P., P.S., A.M., A.B., and G.K. The following authors received funding by Spero Therapeutics provided unrestricted research grant via its Investigator initiated research program, B.F., M.R., P.V., S.H., G.S., D.Z., G.H., M.C., C.T., M.J., T.F., and D.T. REDCap database was supported by the National Center for Advancing Translational Sciences of the National Institutes of Health under Award Number UL1TR002537. CB was partially funded by a research grant from the Mayo Midwest Pharmacy Research Committee.

PRESENTATION

This work was accepted and presented at IDWeek Virtual Conference: 2021.

ORCID

Brett A. Faine https://orcid.org/0000-0002-5759-9857
Alan Gross https://orcid.org/0000-0001-9352-8389
David Zimmerman https://orcid.org/0000-0002-9661-0895
Anne Zepeski https://orcid.org/0000-0001-6309-6554
Matt Campbell https://orcid.org/0000-0001-7698-477X
Cierra N. Treu https://orcid.org/0000-0002-9558-5499
David A. Talan https://orcid.org/0000-0002-7048-8086

REFERENCES

1. Takhar SS, Moran GJ. Diagnosis and management of urinary tract infection in the emergency department and outpatient settings. *Infect Dis Clin North Am*. 2014;28:33-48.
2. Gupta K, Grigoryan L, Trautner B. Urinary tract infection. *Ann Intern Med*. 2017;167:ITC49-ITC64.
3. Foxman B. The epidemiology of urinary tract infection. *Nat Rev Urol*. 2010;7:653-660.
4. Foxman B. Urinary tract infection syndromes: occurrence, recurrence, bacteriology, risk factors, and disease burden. *Infect Dis Clin North Am*. 2014;28:1-13.
5. Talan DA, Takhar SS, Krishnadasan A, et al. Fluoroquinolone-resistant and extended-Spectrum β-lactamase-producing Escherichia coli infections in patients with pyelonephritis, United States(1). *Emerg Infect Dis*. 2016;22:1594-1603.
6. Talan DA, Takhar SS, Krishnadasan A, et al. Emergence of extended-Spectrum β-lactamase urinary tract infections among hospitalized emergency department patients in the United States. *Ann Emerg Med*. 2021;77:32-43.
7. Gupta K, Hooton TM, Naber KG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. *Clin Infect Dis*. 2011;52:e103-e120.
8. Core Elements of Hospital Antibiotic Stewardship Programs. Centers for Disease Control and Prevention. 2019. 2021. https://www.cdc.gov/antibiotic-use/healthcare/pdfs/hospital-core-elements-H.pdf
9. Antibiotic Resistance Threats in the United States. 2019. 2021. https://www.cdc.gov/drugresistance/biggest-threats.html
10. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Int J Surg*. 2014;12:1495-1499.
11. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42:377-381.
12. Hooton TM. Uncomplicated urinary tract infection. *New England Journal of Medicine*. 2012;366:1028-1037.
13. Abrahamian FM, Moran GJ, Talan DA. Urinary tract infections in the emergency department. *Infect Dis Clin North Am*. 2008;22(73–87):vi-87.
14. Jackson GG, Grieble HG, Knudsen KB. URINARY FINDINGS DIAGNOSTIC OF PYELONEPHRITIS. *Jama*. 1958;166:14-17.
15. McCarter Y, Burd EM, Hall GS, Zervos M. *Cumitech 2c: Laboratory Diagnosis of Urinary Tract Infections*. AMS Press; 2009.
16. Burd EM, Kehl KS. A critical appraisal of the role of the clinical microbiology Laboratory in the Diagnosis of urinary tract infections. *J Clin Microbiol*. 2011;49:S34-S38.
17. Wilson C. *Clinical Microbiology Procedures Handbook*. 4th ed. AMS Press; 2016.
18. Jorgensen S, Zurayk M, Yeung S, et al. Emergency department urinary antibiograms differ by specific patient group. *J Clin Microbiol*. 2017;55:2629-2636.
19. Tenney J, Hudson N, Alnifaidy H, Li JTC, Fung KH. Risk factors for aquiring multidrug-resistant organisms in urinary tract infections: a systematic literature review. *Saudi Pharm J*. 2018;26:678-684.
20. Zhanel GG, Hisanaga TL, Laing NM, et al. Antibiotic resistance in Escherichia coli outpatient urinary isolates: final results from the north American urinary tract infection collaborative Alliance (NAUTICA). *Int J Antimicrob Agents*. 2006;27:468-475.
21. Sanchez Guillermo V, Master Ronald N, Karlowsky James A, Bordon JM. In Vitro Antimicrobial Resistance of Urinary Escherichia coli Isolates among U.S. Outpatients from 2000 to 2010. *Antimicrob Agents Chemother*. 2012;56:2181-2183.
22. Pitout JDD, Laupland KB. Extended-spectrum β-lactamase-producing Enterobacteriaceae: an emerging public-health concern. *Lancet Infect Dis*. 2008;8:159-166.
23. Kaye KS, Gupta V, Mulgirigama A, et al. Antimicrobial Resistance trends in urine Escherichia coli isolates from adult and adolescent females in the United States from 2011 to 2019: rising ESBL strains and impact on patient management. *Clin Infect Dis*. 2021;73:1992-1999.
24. Doi Y, Park YS, Rivera JI, et al. Community-associated extended-spectrum β-lactamase-producing Escherichia coli infection in the United States. *Clin Infect Dis*. 2013;56:641-648.
25. Faine BA, Harland KK, Porter B, Liang SY, Mohr N. A clinical decision rule identifies risk factors associated with antimicrobial-resistant urinary pathogens in the emergency department: a retrospective validation study. *Ann Pharmacother*. 2015;49:649-655.
26. Frazee BW, Trivedi T, Montgomery M, Petrovic D-F, Yamaji R, Riley L. Emergency department urinary tract infections caused by extended-Spectrum β-lactamase–producing Enterobacteriaceae: many patients have no identifiable risk factor and discordant empiric therapy is common. *Ann Emerg Med*. 2018;72:449-456.
27. Khawcharoenporn T, Vasoo S, Singh K. Urinary tract infections due to multidrug-resistant Enterobacteriaceae: prevalence and risk factors in a Chicago emergency department. *Emerg Med Int*. 2013;2013:258517.
28. Taylor RA, Moore CL, Cheung K-H, Brandt C. Predicting urinary tract infections in the emergency department with machine learning. *PLoS One*. 2018;13:e0194085.

How to cite this article: Faine BA, Rech MA, Vakkalanka P, et al. High prevalence of fluoroquinolone-resistant UTI among US emergency department patients diagnosed with urinary tract infection, 2018–2020. *Acad Emerg Med*. 2022;29:1096-1105. doi: 10.1111/acem.14545